

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant :David BROWN et al. **Confirmation No. 4047**
Appl. No. :10/736,902 Group Art Unit: 1615
Filed :December 17, 2003 Examiner: Sheikh, Humera N.
For :DOSAGE FORM CONTAINING PROMETHAZINE AND ANOTHER DRUG

REPLY BRIEF UNDER 37 C.F.R. § 41.41(a)(1)

Commissioner for Patents
U.S. Patent and Trademark Office
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Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

This Reply Brief is in response to the Examiner's Answer mailed May 14, 2009, the period for reply extending until July 14, 2009.

In the Examiner's Answer all grounds of rejection set forth in the final rejection are maintained.

Appellants note that the Examiner's Answer does not sufficiently address several of Appellants' arguments as to why the rejections are without merit, and misrepresents some of the facts. These deficiencies have prompted the present Reply Brief.

Appellants also note that this Reply Brief is being filed under 37 C.F.R. § 41.41(a)(1) and is directed to the arguments presented in the Examiner's Answer, and therefore must be entered unless the final rejection is withdrawn in response to the instant Reply Brief.

In order to avoid repetition, the following response to the Examiner's arguments in the Examiner's Answer will be limited to issues which are important enough to warrant a further comment in Appellants' opinion. Accordingly, Appellants' silence with respect to any allegations set forth in the Examiner's Answer which are not specifically addressed below should by no means be construed as Appellants' admission that these allegations are of any merit.

REPLY

1. As an initial matter and to avoid any possible misunderstanding regarding the subject matter of the present claims, Appellants point out that the present claims are not concerned merely with a period over which there is a measurable plasma concentration of a first drug (promethazine in the case of independent claims 1 and 27, an antihistamine in the case of independent claim 68) in relation to the period over which there is a measurable plasma concentration of the at least one second drug. Rather, the present claims recite a period over which there is a plasma concentration of the first drug within the therapeutic range (i.e., the period during which the first drug shows a therapeutic effect) in relation to the period over which there is a plasma concentration of the at least one second drug within the therapeutic range (i.e., the period during which the second drug shows a therapeutic effect).

In other words, according to the present claims it is not sufficient that (i) there is a measurable plasma concentration of the at least one second drug over a period which

coincides with at least about 70 % of the period over which there is a measurable plasma concentration of the first drug and/or (ii) that the dosage form releases the at least one second drug over a period which coincides with at least about 70 % of the period over which the dosage form released the first drug. Rather, according to, e.g., present claim 1 the at least one second drug must show a therapeutic effect over at least about 70 % of the period over which the first drug shows a therapeutic effect.

For example, the at least one second drug may show a measurable plasma concentration over 100 % of the period over which there is (also) a measurable plasma concentration of the first drug, or even over 100 % of the period over which the first drug shows a plasma concentration within the therapeutic range (shows a therapeutic effect). Nevertheless, the plasma concentration of the at least one second drug – while measurable – may still only be high enough to give rise to a therapeutic effect for, say, 30 % of the period over which the plasma concentration of the first drug is high enough to give rise to a therapeutic effect. Since present claim 1, for example, recites a corresponding percentage of at least about 70 %, this scenario would not be encompassed by claim 1.

Accordingly, the concept reflected by the present claims is much more sophisticated than the Examiner may have appreciated.

2. Appellants point out again that it is not seen that in view of the passage of Fanara et al., U.S. Patent No. 6,699,502 (hereafter "FANARA") which the Examiner appears to primarily rely on, i.e., col. 2, lines 36-50, one of ordinary skill in the art would have an apparent reason to provide a dosage form which comprises two different active

substances (at least one of them being promethazine or an antihistamine in general) which releases the two active substances in such a manner that the plasma concentration of one active substance is within the therapeutic range over a period which is coextensive with at least about 70 % of the period over which the plasma concentration of the other active substance is within the therapeutic range.

The passage of FANARA primarily relied on by the Examiner makes reference to active substances having “very different pharmacokinetic profiles” which can be administered by means of the immediate/controlled release formulations described therein. FANARA does not explain what is to be understood by the phrase “very different pharmacokinetic profiles”. However, according to http://www.nature.com/nrg/journal/v4/n10/glossary/nrg1180_glossary.html

“pharmacokinetic profile” is a very vague term, i.e., is defined as “[t]he characteristics of a drug that determine its absorption, distribution and elimination in the body”. The Examiner has again failed to explain why one of ordinary skill in the art knowing that the immediate/controlled release combinations set forth in FANARA make it possible to obtain combined therapeutic effects by means of two active substances which have very different characteristics that determine their absorption, distribution and elimination in the body would find it obvious to provide an immediate/controlled release combination according to FANARA for providing plasma concentrations in a therapeutic range of these two active substances in a manner such that the therapeutically effective period of one drug coincides with at least about 70 % of the therapeutically effective period of the other drug. The Examiner has again failed to provide any written (or other) evidence whatsoever which would show that there is an (apparent) link between the different

characteristics which determine absorption, distribution and elimination in the body of two drugs and the difference in the duration of action of one of these drugs in relation to the duration of action of the other one of these drugs.

In this regard, it further is pointed out again that there is not a single passage in FANARA wherein the duration of action of one active substance in relation to the duration of action of another active substance is addressed. Whenever combinations of active substances are mentioned in FANARA these combinations are to be contained in immediate release/controlled release dosage forms, i.e., dosage forms which are designed for the sole purpose of providing different release rates and/or release periods of the active substances, i.e., without any concern regarding the time and duration of action of one active substance in relation to the time and duration of action of the other active substance. This fact alone makes it apparent that FANARA is unable to render obvious the subject matter of any of the present claims.

3. At page 9, third paragraph of the Examiner's Answer the Examiner alleges:

...Appellants are not claiming a specific drug release profile of the first and second active substances with respect to time, which would patentably define and distinguish over the release rates suggested by [FANARA]. Moreover, as noted above, [FANARA] employs and teaches multi-layered dosage forms comprised of various active substances and achieves therapeutically-effective results using the same. Thus the results sought by Appellant are achieved by the prior art. Furthermore, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., duration of action in relation to time) are not recited in the rejected claim(s). . .

In response, Appellants point out again that while it is correct that the present claims do not recite the duration of action of any specific active substance, they clearly recite the duration of action of one active substance (the at least one second drug) in

relation to the duration of action of another active substance (the first drug). In other words, claim 1, for example, recites "the dosage form provides a plasma concentration within a therapeutic range of the at least one second drug over a period which is coextensive with at least about 70 % of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug". This recitation can also be worded differently by stating that the at least one second drug exhibits a therapeutic effect for at least about 70 % of the time during which the first drug (promethazine, antihistamine) exhibits a therapeutic effect, or by stating that in relation to the period over which the first drug exhibits a therapeutic effect the at least one second drug exhibits a therapeutic effect for at least 70 % of this period.

4. The Examiner also alleges that "the limitation 'over a period which is coextensive...' is vague in that it does not refer to any specific extent or duration over which the plasma concentration of the first and second active substance should overlap."

See, e.g., page 13, second paragraph of the Examiner's Answer.

Appellants submit that this assertion is clearly without merit as well. Claim 1, for example, expressly recites the "extent or duration over which the plasma concentration of the first and second active substance should overlap", i.e., that for at least about 70 % of the duration of action of the first drug the at least one second drug also exhibits a therapeutic effect.

5. In the paragraph bridging pages 11 and 12 of the Examiner's Answer the Examiner alleges with respect to claim 68 and the difference in plasma half-lives of at least about 3 hours between the first and second drug recited therein:

... it is noted that the primary reference of [FANARA] initially teaches similar active ingredients as claimed and thus, the difference in the plasma half-lives would be expected to be the same as that claimed herein by Appellant. For example, co-administration of Fanara's active substances would yield the same plasma parameters sought by Appellant. The difference in the drug plasma half-lives would be the same and would be inherent based on the teachings of the prior art which represents administration of the same active substances. The prior art would also provide for overlap or coextension of drug activity, absent a showing of evidence to the contrary."

A similar assertion is found, e.g., at page 10, second paragraph, page 12, third paragraph, and in the paragraph bridging pages 25 and 26 of the Examiner's Answer.

In this regard, Appellants note that the Examiner has not provided any evidence whatsoever which would support the above allegations. Also, Appellants do not know how the Examiner assesses whether or not two active ingredients are "similar". Should the Examiner refer to structural similarity (by whichever standard this similarity is to be assessed), Appellants are not aware that active ingredients which are structurally "similar" have "similar" half-lives, and neither has the Examiner provided any explanation or evidence in this regard. Should the Examiner refer to similarity in terms of the type of therapeutic activity elicited by two drugs, Appellants are also not aware that two drugs which have a similar therapeutic activity have "similar" half-lives and note that the Examiner has not provided any explanation or evidence in this regard, either.

Moreover, it is pointed out that the present claims are not directed to merely any overlap or coextension of the activity of any two drugs but to an overlap or coextension of drug activity of at least about 70 % with respect to an antihistamine and at least one

second drug which has a half-life which differs from the half-life of the antihistamine by at least about 3 hours and is selected from certain classes of drugs (see, e.g., claim 68).

6. Appellants further note that the Examiner alleges that the criticality of certain elements which are recited in the present claims has not been shown. See, for example, page 10, end of second paragraph, of the Examiner's Answer with respect to the recited difference in plasma half-lives between the first drug and the at least one second drug.

In response, Appellants point out that there is no need to show the criticality of these elements because the Examiner has failed to establish that it would have been *prima facie* obvious for one of ordinary skill in the art to provide a dosage form as recited in the present claims and in particular, a dosage form which comprises these elements (let alone in combination).

7. At the beginning of page 11 of the Examiner's Answer the Examiner alleges that FANARA (probably FINDLAY = U.S. Patent No. 4,650,807 was intended) "demonstrates the general teaching that the use of antihistamines is well known, albeit, with certain side effects. The reference teaching, nonetheless, would not deter one of ordinary skill in the art from using the particular antihistamines for their known beneficial effects, i.e., histamine antagonistic effects."

Appellants point out that the question here is not whether or not FINDLAY deters one of ordinary skill in the art from including promethazine in the compositions according to FANARA, but whether or not FINDLAY provides an apparent reason for one of ordinary skill in the art to do so. Given the fact that FINDLAY points out that

antihistamines such as pheniramines and promethazine "exhibit varying degrees of anticholinergic activity" which "causes dryness of mouth, blurred vision and tachycardia and is generally regarded as undesirable" it is not seen that FINDLAY provides any such apparent reason. In fact, the entire disclosure of FINDLAY focuses on avoiding the use of an antihistamine such as promethazine.

8. In the paragraph bridging pages 24 and 25 of the Examiner's Answer the Examiner alleges, *inter alia* (emphasis added):

... A review of the present specification establishes that the plasma concentration (of promethazine) being within a therapeutic range for at least about 24 hours per single dose is achieved as a result of the use of layered (i.e., bi-layered) dosage formulations having varied release rates (immediate release, controlled release). The prior art applies the same technique as that of the instant invention. Namely, the prior art of record explicitly teaches multi-layered dosage formulations comprising one or more active substances whereby the first layer of active substance is provided in immediate release form and the second layer is provided in controlled release form. See, for instance, Example 7 at column 12 of [FANARA], which amply demonstrates a double-layered tablet comprising hydrocodone bitartrate. ... Thus, the prior art vividly recognizes and teaches the use of multi-layered dosage forms which deliver active agents in both immediate as well as controlled/sustained release. Since the same technique is utilized by the prior art to provide effective therapeutic effects, as is desired by Appellant, it cannot be seen how the prior art would not obtain an effective plasma concentration of a drug....

Appellants submit that it is not seen that anywhere in the present specification it is established "that the plasma concentration (of promethazine) being within a therapeutic range for at least about 24 hours per single dose is achieved as a result of the use of layered (i.e., bi-layered) dosage formulations having varied release rates (immediate release, controlled release)". Moreover, even if the present specification were to any contain disclosure in this respect, it is unclear how this would affect the patentability of

the subject matter of any of the present claims and in particular, of claim 27 (specifically referred to by the Examiner in this regard).

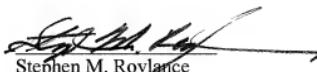
Appellants further point out that it is apparent that the mere fact that immediate/controlled release bi-layered tablets are known clearly does not establish that each and every bi-layered tablet will afford the relationship in terms of duration of therapeutically effective plasma concentrations of any two drugs that is recited in, e.g., present claim 27.

CONCLUSION

The request to reverse the rejection of claims 1-24, 27-38 and 68-74 and to return the application to the Examining Group for prompt allowance is respectfully maintained.

Although no fee is believed to be required for entry of this Reply Brief, the Patent and Trademark Office is hereby authorized to charge any fee that is deemed to be necessary to Deposit Account No. 19-0089.

Respectfully submitted,
David BROWN et al.



Stephen M. Roylance
Reg. No. 31,296

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GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191